Opdivo (Nivolumab): Second PD-1 Inhibitor Receives FDA Approval for Unresectable or Metastatic Melanoma

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Although less common than other skin cancers, melanoma is the most dangerous form of skin cancer.[1] According to data collected between 2004 and 2010, the 5-year relative survival rate for Americans with distant melanoma is only 16% for all ages, races, and sexes.[2] The National Cancer Institute estimated that there were 76,100 new cases of skin melanoma in 2014, and more than 9700 patients died from this disease during the same period.[2] The incidence of melanoma continues to rise, particularly among children and adolescents.[3] Analysis of first-time melanoma diagnoses between 1970 and 2009 in patients aged 18 to 39 years showed that the number of new cases of skin melanoma increased 8-fold among young women and 4-fold among young men.[3] Using data from 1973 to 2009, another study documented an average increase in melanoma of 2% annually in individuals aged between 0 and 19 years.[4]

The potential effect on healthcare resource use is just one reason for concern regarding these trends. Based on an assessment of Medicare administrative claims data between 1991 and 2005, patients with melanoma, particularly those with metastatic disease, accrued an average of more than $11,000 monthly in total healthcare costs[5]; the majority of these costs were related to inpatient hospital services.[5] This cost analysis was conducted in 2009, before the approval of novel targeted therapies for metastatic melanoma.

As evidenced by its low 5-year survival rates, metastatic melanoma is difficult to cure.[6] Surgery and radiation therapy are feasible options for tumors that are localized to the skin or to the lymph nodes. Depending on their number and location, the surgical removal of melanoma metastases in internal organs is also an option.[6]

In the past, the management of patients with advanced stages of melanoma was very challenging. Today, however, the development and the introduction of targeted agents have significantly changed the treatment landscape. The current armamentarium of systemic treatments for metastatic melanoma features immunotherapy agents (ie, ipilimumab, pembrolizumab) and BRAF inhibitors (ie, vemurafenib, dabrafenib, trametinib), in addition to traditional chemotherapy.[6] Several of these novel agents offer superior efficacy compared with older cytotoxic drugs.[6]

Immune checkpoint blockade with monoclonal antibodies that are directed toward cytotoxic T-lymphocyte antigen (CTLA)-4, such as ipilimumab, as well as programmed-cell death (PD)-1 and PD ligand 1 (PD-L1), have emerged as successful treatment options in the treatment of patients with melanoma.[7] Ipilimumab was the first CTLA-4 inhibitor to demonstrate an overall survival benefit and highly durable objective tumor responses in patients with advanced melanoma.[7]

In September 2014, the US Food and Drug Administration (FDA) approved pembrolizumab, the first PD-1 inhibitor for the treatment of patients with unresectable or metastatic melanoma.[8] This agent demonstrated objective and durable responses in a large phase 1b study that involved patients with unresectable or metastatic melanoma and disease progression after treatment with ipilimumab and, if the patient had the *BRAF* V600 mutation, after treatment with a BRAF inhibitor.[8,9] To increase the proportion of patients with metastatic melanoma who achieve durable responses with immunotherapy, researchers are exploring potential synergies between immune checkpoint inhibitors that target CTLA-4, PD-1, PD-L1, and kinase-targeted therapies, as well as the concurrent and sequential use of CTLA-4, PD-1, and PD-L1 inhibitors.[7]

A Novel PD-1 Inhibitor for Advanced Melanoma

On December 22, 2014, the FDA approved nivolumab (Opdivo; Bristol-Myers Squibb) for the treatment of patients with unresectable or metastatic melanoma and disease progression after ipilimumab therapy and, if the patient is positive for a *BRAF* V600 mutation, after treatment with a BRAF inhibitor.[10,11] Nivolumab is a monoclonal antibody that blocks PD-1 and is administered via intravenous infusion. This agent was approved under the accelerated approval program based on the surrogate end points, overall response rate, and duration of response.[10,11]

When discussing data supporting the efficacy of nivolumab in relapsed metastatic melanoma, Jeffrey S. Weber, MD, PhD, Director of the Donald A. Adam Comprehensive Melanoma Research Center of Excellence at Moffitt Cancer Center, stated, "These data are important as they mark the first presentation of results from a phase 3 randomized study for the PD-1 immune checkpoint inhibitor class. The response rate and duration of response in pa-

tients treated with Opdivo are consistent with findings from the early phase 1 trial in previously treated advanced melanoma."[12] In March 2015, nivolumab received a new FDA indication for lung cancer. See page 183.

Dosing and Administration

The recommended dosage of nivolumab is 3 mg/kg administered as an intravenous infusion for 60 minutes every 2 weeks. Nivolumab should be administered until disease progression or until unacceptable toxicity.[11]

No dose adjustment of nivolumab is required for patients with renal impairment or for patients with mild hepatic impairment, defined as total bilirubin upper limit of normal or less and aspartate aminotransferase (AST) more than upper limit of normal or total bilirubin <1 to 1.5 times upper limit of normal and any AST.[11]

Mechanism of Action

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks interaction with its ligands, PD-L1 and PD-L2. This binding releases PD-1 pathway-mediated immune responses against tumor cells. Blocking PD-1 activity resulted in decreased tumor growth in syngeneic mouse tumor models.[11]

Clinical Trial: Checkmate-037

The approval of nivolumab was based on the results of Checkmate-037, a phase 3 randomized, controlled, open-label study of nivolumab versus investigator's choice chemotherapy in patients with advanced melanoma who previously received ipilimumab.[11] A total of 370 patients with previously treated unresectable or metastatic melanoma enrolled in the Checkmate-037 clinical trial.[11] All patients' disease had progressed after previous therapy with ipilimumab and, if the patients were positive for a *BRAF* V600 mutation, after treatment with a BRAF inhibitor.[11] These patients were randomized to receive nivolumab 3 mg/kg (N = 268) or investigator's choice chemotherapy (N = 102) with dacarbazine 1000 mg/m^2 every 3 weeks or with carboplatin (area under the curve, 6 mg•min/mL) plus paclitaxel 175 mg/m^2 every 3 weeks until disease progression or until unacceptable toxicity.[11]

The efficacy of nivolumab was evaluated in a single-arm, noncomparative, planned interim analysis of the first 120 patients who received nivolumab in the Checkmate-037 clinical trial and in whom the minimum duration of follow-up was 6 months.[11] The primary efficacy end points were confirmed overall response rate according to the Response Evaluation Criteria in Solid Tumors, as assessed by a blinded independent review committee, and duration of response. Tumor assessments were conducted 9 weeks after randomization, followed by every 6 weeks for the first year, and then every 12 weeks.[11]

The trial excluded patients with an autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled after 12 weeks.[11]

Among the 120 patients who received nivolumab, the median age was 58 years.[11] The majority of the patients were male (65%) and white (96%). All the patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. The patients' disease characteristics included stage M1c disease (76%), 2 or more previous therapies for advanced or metastatic disease (68%), elevated lactate dehydrogenase (56%), positive for a *BRAF* V600 mutation (22%), and a history of brain metastases (18%).[11]

The planned interim analysis of the Checkmate-037 clinical trial documented a 32% overall response rate for nivolumab 3 mg/kg in patients with unresectable or metastatic melanoma who previously received ipilimumab therapy and, if relevant, a BRAF inhibitor (95% confidence interval, 23%-41%).[11] Of the 38 patients whose disease responded to nivolumab therapy, 4 patients achieved complete responses and 34 patients achieved partial responses.[11] The majority (87%) of patients responding to nivolumab had ongoing responses with durations ranging from 2.6+ to 10+ months, including 13 patients with ongoing responses of at least 6 months.[11]

Adverse Events

The cohort of 268 patients with previously treated unresectable or metastatic melanoma in Checkmate-037 received a median of 8 doses (range, 1-31 doses) of nivolumab (3 mg/kg).[11] The patients' median duration of exposure to nivolumab was 5.3 months (range, 1 day-9.6 months).[11] Overall, 24% of patients were exposed to nivolumab for more than 6 months, and 3% of patients were exposed to nivolumab for more than 1 year.[11]

The **Table** summarizes the adverse reactions that occurred in ≥10% of patients and at a higher incidence rate compared with patients who received chemotherapy.[11]

Grade 3 and 4 adverse reactions occurred in 42% of nivolumab recipients.[11] These events included abdominal pain, hyponatremia, elevated AST levels, and increased lipase levels; these adverse reactions occurred at rates ranging from 2% to <5%.[11] Nivolumab was discontinued as a result of adverse reactions in 9% of patients, and 26% of patients who received nivolumab experienced a drug delay for an adverse reaction.[11]

Nivolumab has no contraindications.

Warnings and Precautions

Immune-mediated pneumonitis. Overall, 5 (0.9%)

fatal cases of pneumonitis occurred among 574 patients with solid tumors who received nivolumab in clinical trials.[11] Pneumonitis, including interstitial lung disease, occurred in 3.4% of patients who received nivolumab in the Checkmate-037 clinical trial.[11] Immune-mediated pneumonitis, which requires the use of corticosteroids and has no clear alternate etiology, occurred in 6 (2.2%) patients who received nivolumab. Grade 2 pneumonitis led to discontinuation of nivolumab in 4 patients. The other 2 patients discontinued nivolumab for other reasons. In all 6 patients, immune-mediated pneumonitis improved to grade 0 or 1 with corticosteroids.[11] Patients should be monitored for pneumonitis. Corticosteroids should be administered if grade 2 or higher pneumonitis is detected.[11] Nivolumab should be withheld for moderate (grade 2) pneumonitis, and permanently discontinued for severe (grade 3) or life-threatening (grade 4) pneumonitis.[11]

Immune-mediated colitis. Colitis or diarrhea occurred in 21% of patients who received nivolumab, and in 18% of patients who received chemotherapy.[11] Immune-mediated colitis was observed in 6 patients who received nivolumab.

Patients should be monitored for colitis. Corticosteroids should be administered for grade 2 or higher colitis. Nivolumab should be withheld for grade 2 or grade 3 colitis, and permanently discontinued for grade 4 colitis or recurrent colitis upon restarting nivolumab therapy.[11]

Immune-mediated hepatitis. An increased incidence of liver test abnormalities was observed in the nivolumab group compared with the chemotherapy group, including increases in AST levels (28% vs 12%, respectively), alkaline phosphatase levels (22% vs 13%, respectively), alanine aminotransferase levels (16% vs 5%, respectively), and total bilirubin levels (9% vs 0%, respectively).[11] Overall, 1.1% of patients who received nivolumab had immune-mediated hepatitis, which requires the use of corticosteroids and has no clear alternate etiology.[11] Nivolumab should be withheld if grade 2 hepatitis is observed, and discontinued for grade 3 and grade 4 immune-mediated hepatitis.[11]

Table Selected Adverse Reactions in ≥10% of Patients Receiving Nivolumab (and at a Higher Incidence than in the Chemotherapy Arm)

Adverse reaction	Nivolumab 3 mg/kg every 2 weeks (N = 268)		Chemotherapy (N = 102)	
	All grades, %	Grade 3-4, %	All grades, %	Grade 3-4, %
Skin and subcutaneous tissue disorders				
Rash[a]	21	0.4	7	0
Pruritus	19	0	3.9	0
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	6	0
Infections and infestations				
Upper respiratory tract infection[b]	11	0	2.0	0
General disorders and administration site conditions				
Peripheral edema	10	0	5	0

[a]Including maculopapular, erythematous, pruritic, follicular, macular, papular, pustular, or vesicular rash, and dermatitis acneiform.
[b]Including rhinitis, pharyngitis, and nasopharyngitis.
Source: Opdivo (nivolumab) injection prescribing information; December 2014.

Immune-mediated nephritis/renal dysfunction. An increased incidence of elevated creatinine levels was observed in patients who received nivolumab compared with patients who received chemotherapy (13% vs 9%) in the Checkmate-037 clinical trial.[11] Grade 2 or 3 immune-mediated nephritis or renal dysfunction, defined as grade 2 or higher increased creatinine levels, need for corticosteroids, and no clear etiology, occurred in 0.7% of patients after 3.5 months and 6 months of nivolumab therapy, respectively.[11]

Patients should be monitored for elevated serum creatinine levels before and during treatment with nivolumab.[11] If grade 4 elevation in serum creatinine levels is observed, corticosteroid therapy should be tapered and nivolumab should be permanently discontinued. Nivolumab therapy should be withheld if grade 2 or 3 elevation in serum creatinine levels is observed.[11]

Immune-mediated hypothyroidism and hyperthyroidism. Grade 1 or 2 hypothyroidism occurred in 8% of patients who received nivolumab and was not observed among patients who received chemotherapy. The median time to onset was 2.5 months (range, 24 days-11.7 months). The majority of patients with hypothyroidism received levothyroxine and restarted nivolumab therapy.[11] Grade 1 or 2 hyperthyroidism occurred in 3% of patients who received nivolumab and in 1% of patients who received chemotherapy. The median time to onset in patients who received nivolumab was 1.6 months (range, 0-3.3 months).[11] Thyroid function should be monitored before and during treatment with nivolumab. Hormone replacement therapy for hypothyroidism should be administered as needed, and hyperthyroidism should be controlled. There are no recommended dose adjustments for nivolumab.[11]

Other immune-mediated adverse reactions. Other clinically important immune-mediated adverse reactions can occur while patients with unresectable or metastatic melanoma are receiving nivolumab.[11] Clinically significant, immune-mediated adverse reactions that were observed in <1% of patients who received nivolumab included pancreatitis, uveitis, demyelination, autoimmune neuropathy, adrenal insufficiency, and facial and abducens nerve paresis.[11]

When nivolumab was administered at doses of 3 mg/kg and 10 mg/kg, clinically significant, immune-mediated adverse reactions were observed, including hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome.[11] If an immune-mediated adverse reaction is suspected, patients who receive nivolumab must be evaluated to exclude other causes.[11]

Embryofetal toxicity. Nivolumab therapy may cause fetal harm when it is administered to a pregnant woman.[11] Women of reproductive potential should use effective contraception during nivolumab therapy and for at least 5 months after the last dose. Women who become pregnant while taking nivolumab should be made aware of the potential risk of nivolumab to the fetus.[11]

Use in Specific Populations

Pediatric patients. The safety and efficacy of nivolumab in pediatric patients have not been established.[11]

Geriatric use. The clinical studies of nivolumab did not include sufficient numbers of patients aged ≥65 years to determine whether they respond differently compared with younger patients.[11]

Pregnancy. There are no human data to describe the risk associated with nivolumab use during pregnancy. Pregnant women should be advised of the potential risk of nivolumab therapy to the fetus.[11]

Nursing mothers. It is not known whether nivolumab is present in human milk. Because many drugs, including antibodies, are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from nivolumab, women should be advised to discontinue breastfeeding during treatment with nivolumab.[11]

Conclusion

Nivolumab is the second PD-1 inhibitor approved by the FDA for the treatment of patients with unresectable or metastatic melanoma. Based on an interim analysis of phase 3 clinical data, this novel agent is an effective and safe alternative for patients with unresectable or metastatic melanoma and disease progression after ipilimumab therapy, and if the patient is positive for a *BRAF* V600 mutation, after treatment with a BRAF inhibitor. As a condition of its accelerated approval, the FDA requires confirmatory trials to verify the agent's clinical benefit.

The new indication for nivolumab approved by the FDA for the treatment of patients with metastatic NSCLC adds a new treatment options for patients with this hard-to-treat disease. The efficacy and safety of nivolumab are being evaluated in several other tumors; these include metastatic breast cancer, metastatic colon cancer, follicular lymphoma, Hodgkin lymphoma, and non-Hodgkin lymphoma.[13] ■

Nivolumab Approved for Metastatic Lung Cancer

On March 4, 2015, the FDA approved a new indication for nivolumab for the treatment of patients with metastatic squamous non–small-cell lung cancer (NSCLC) that had progressed with platinum-based chemotherapy. "This approval will provide patients and health care providers knowledge of the survival advantage associated with Opdivo," said Richard Pazdur, MD, Director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research.

The efficacy of nivolumab in squamous NSCLC was demonstrated in a clinical trial of 272 patients with squamous NSCLC who were randomized to nivolumab (N = 135) or to docetaxel (N = 137). The overall survival was an average of 3.2 months longer with nivolumab than with docetaxel. The safety and efficacy of nivolumab for the treatment of squamous NSCLC were further seen in a single-arm trial of 117 patients with squamous NSCLC that had progressed after platinum-based therapy and ≥1 additional systemic regimens. The objective response rate was 15%, all partial responses. At the time of the analysis, 10 of the 17 responding patients (59%) had a response duration lasting ≥6 months.

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